[19]中华人民共和国专利局

[51]Int.Cl[6]
C07H 17/08

[12] 发明专利申请公开说明书

[21] 申请号 97101204.0

[43]公开日 1997 年 10 月 15 日

[11] 公开号 CN 1161971A

[22]申请日 97.1.3
[71]申请人 石家庄制药集团有限公司
地址 050051河北省石家庄市中山西路276号
[72]发明人 殷殿书

[74]专利代理机构 河北省专利事务所
代理人 蔡德成 申东民

权利要求书 1 页 说明书 4 页 附图页数 0 页

[54]发明名称 一种阿齐霉素结晶及其制备方法

[57]摘要

本发明涉及一种阿齐霉素结晶及其制备方法，它主要是由含水阿齐霉素溶于水溶性有机溶剂和水的混合物中结晶、干燥后获得的非二水结晶型阿齐霉素。本发明解决了现有技术制得的产品性质不稳定、生产困难、成本高等缺点，具有产品稳定性能较国外进口产品好，流动性强，易于工业化生产，制备方法简单，试剂易于得到等优点。

权 利 要 求 书

1、一种阿齐霉素结晶，其特征在于在室温条件下含有低于4%的吸附水。

2、 根据权利要求1所述的阿齐霉素结晶， 其特征在于它具有如下特征：紫外吸收光谱最大吸收波长λmax=207.7nm，核磁共振氢谱 ^{1}H—NMR (CDCl2) δ:2.28 [3′—N (CH3) 2]，2.34 (9a—NCH3)，核磁共振碳谱 ^{13}C—NMR(CDCl3) δ:178.91(C—1)，78.14和83.32(C—3，C—5)，36.14(9a—NCH3)，40.34 [3′—NC(CH3)2]，红外光谱：利用溴化钾法测定本品在3600—3400cm^{-1}，3020—2780cm^{-1}，1719cm^{-1}，1460—1340cm^{-1}，1380cm^{-1}及1200—1000cm^{-1}处有特征吸收峰。

3、根据权利要求1所述的阿齐霉素结晶的制备方法，其特征是用含水阿齐霉素溶于水溶性有机溶剂和水的混合物中进行结晶后干燥得到的。

4、根据权利要求3所述的方法，其特征在于其中含水阿齐霉素：水：水溶性有机溶剂的相对重量比为1：30—1000：9—16。

5、根据权利要求3或4所述的方法，其特征在于水溶性有机溶剂可以是乙醇、丙酮、异丙醇、丙醇、1.2—丙二醇、1.3—丙二醇、丙腈、2—氯乙醇，N，N，N′，N′—四甲基脲，N—甲基吡咯烷酮，烯丙醇或上述物质的混合物中的一种。

6、根据权利要求4所述的方法，其特征在于有机溶剂优选丙酮、乙醇或它们的混合物。

7、根据权利要求3所述的方法，其特征在于干燥为真空干燥，时间为4—5小时。

说　明　书

一种阿齐霉素结晶及其制备方法

本发明涉及一种阿齐霉素结晶及其制备方法。

阿齐霉素（化学名称为N－甲基－9a－氮杂－9－脱氧－9－二氢红霉素A）衍生于红霉素A，是一种广谱抗生素，阿齐霉素与红霉素相比，具有抗菌谱广，有良好的酸稳定性，利于口服，药代动力学特性理想等优点，美国专利US．4，512，982，US．4，518，590，US．4，328，334和US．4，474，768，US．4517359披露了阿齐霉素合成方法和阿齐霉素含水物的合成方法，即将甲化粗品溶于热乙醇后逐渐加水至溶液稍显混浊，过夜静置从溶液中结晶出阿齐霉素再用同样的方法进行重结晶，该方法不足之处在于：由此做出的阿齐霉素含水物在空气中易吸湿，常温中不易保存，给制剂生产带来了很大困难；欧洲专利EP298650介绍的不吸湿二水结晶型阿齐霉素主要是由四氢呋喃，C5—C7脂肪烃和水混合后作为溶剂对阿齐霉素进行结晶，该方法不足之处在于该方法使用的四氢呋喃及C5—C7脂肪烃试剂价格昂贵，四氢呋喃及C5—C7脂肪烃沸点相差较小，溶剂回收困难。

本发明的目的在于为解决阿齐霉素含水物易吸湿，降低阿齐霉素合水物结晶成本，使阿齐霉素结晶具有更好的流动性和药物制剂具有更高的生物利用度而提供一种阿齐霉素结晶及其制备方法。

本发明的目的之一是提供一种阿齐霉素结晶，其具有良好的流动性和非结晶水含量，具体地说本发明中阿齐霉素结晶含有小于4％的吸附水，具有如下特征：

1、红外吸收光谱（KBr）显示以下特征基团频率

波数 cm^{-1}	基团
1000—1200	C—O—C
1340—1460	$-CH_2$
1719	$-C=O$
1380	$N-CH_3$
2780—3020	$-CH_3$
3400—3600	$-OH$，H_2O

在3600—3400cm^{-1}，3020—2780cm^{-1}，1719cm^{-1}，1460—1340cm^{-1}，1380cm^{-1}，1200—1000cm^{-1}处有特征吸收峰。

2、紫外吸收光谱：

本发明中阿齐霉素结晶最大吸收波长λmax=207.7nm。

3、元素分析：

理论值（%）	C60.93	H9.69	N3.74
实测值（%）	C59.49	H9.87	N3.74

4、热差分析

由样品与进口对照品的DSC曲线作比较，两者的曲线基本一致，但样品的熔化热比进口对照品小一倍，5.83卡／l（样品）和13.14卡／克（进口对照品），说明本发明阿齐霉素（样品）含吸附水。

5、核磁共振谱（NMR）

a、核磁共振氢谱有如下特征：

^{1}H—NMR(CDCl2) δ:2.28 [3′—N(CH3)2], 2.34(9a—NCH3),

b、核磁共振碳谱有以下主要特征：

^{13}C—NMR(CDCl3) δ:178.9!(C—!), 78. 14和83.32(C—3, C—5),
36.14(9a—NCH3), 40.34 [3′—NC(CH3)2]

6、热重分析（TGA）

随温度升高，样品重量在50—105℃呈近平直线的均匀失重。

7、x—射线衍射：

θ°	面间距 d(A)	I／I0	θ°	面间距 d(A)	I／I0
7.58	11.65	7	19.04	4.66	15
7.80	11.33	26	19.62	4.52	12
9.40	9.40	20	20.40	4.35	26
9.80	9.02	100	20.96	4.24	14
10.06	8.79	5	21.76	4.08	10
11.20	7.89	29	22.60	3.93	9
11.42	7.74	9	23.46	3.79	7
11.94	7.41	7	24.52	3.63	8
12.40	7.09	23	24.76	3.60	9

13.94	6.35	11	25.22	3.53	7
15.72	5.63	15	29.50	3.03	5
16.08	5.51	9	31.24	2.86	5
16.58	5.34	8	32.76	2.73	4
18.42	4.81	9	34.86	2.57	4
18.86	4.70	19	35.14	2.55	4

本发明的目的之二在于提供制备该阿齐霉素结晶的方法，它主要用含水阿齐霉素溶于水溶性有机溶剂和水的混合物中进行结晶后干燥得到的。

该制备方法中的详细步骤及工工艺条件是：

其中含水阿齐霉素：水：水溶性有机溶剂的相对重量比为1：30—1000：9—16。

水溶性有机溶剂可以是乙醇、丙酮、异丙醇、丙醇、1．2—丙二醇、1．3—丙二醇、丙腈、2—氯乙醇，N，N，N′，N′—四甲基脲，N—甲基吡咯烷酮，烯丙醇或上述物质的混合物中的一种。

有机溶剂优选丙酮、乙醇或它们的混合物。

干燥为真空干燥，时间为4—5小时。

以下结合实施例对本发明作进一步描述：

本发明中阿齐霉素结晶的稳定性实验结果见下表：（温度：0—32℃，湿度25—80%）

贮存时间（月）	水份（%）
0	3．3
1	3．4
3	3．5
6	3．5
12	3．6
17	3．6

由上述数据结果可以看出，本发明阿齐霉素结晶在0、1、3、6、12、17个月取样测定含水量在3—4%之间，在小于4%范围内，能满足工业化生产的要求。

对实施例中所述阿齐霉素结晶的制备：

（1）按美国专利US4517359，US4474768制备出的含水阿齐霉素100g，在50℃条件下溶于400ml丙酮中逐滴加水至60

CPCH0161523D

Reference cited in the Second Office Action: **CN1161971A**

The Specification

Ajimycin crystal and preparation method thereof

The present invention pertains to an ajimycin crystal and a preparation method thereof.

Ajimycin (chemical name: N-methyl-9a-aza-9-deoxo-9-dihydroerythromycin A) is derived from erythromycin A, and is a broadspectrum antibiotic. Compared with erythromycin, ajimycin has a broader antibiotic spectrum, has brilliant acidic stability, is suitable for oral administration and has perfect pharmacokinetic properties. The U.S. Patents US4,512,982. US4,518,590; US 4,328,334 and US 4,474,768, and US4,517,359 disclose methods for synthesizing ajimycin and the hydrates thereof: dissolving a methylated crude in hot ethanol; adding water gradually until the solution appears slightly turbid; standing the solution overnight, from which ajimycin is crystallized; then recrystallizing ajimycin in the same way. A disadvantage of this method is that the ajimycin hydrate obtained from said method is hygroscopic in air and is not easily preserved at a normal temperature, thus making the preparation production quite difficult. European Patent EP298650 discloses that the non-hygroscopic azithromycin in the form of a dihydrate crystal, which is prepared by crystallization of azithromycin using a mixture of tetrahydrofuran, an aliphatic C5-C7 hydrocarbon and water as the solvent. The disadvantages of this method are that the tetrahydrofuran and aliphatic C5-C7 hydrocarbon are very expensive, and that it is difficult to recover the solvent as the boiling point of tetrahydrofuran and that of the aliphatic C5-C7 hydrocarbon are slightly different.

An object of this invention is to make ajimycin less hygroscopic, to lower the cost for the crystallization of the ajimycin hydrate, to provide the ajimycin crystal with a better fluidity and the pharmaceutical preparation with a higher bioavailability, thus to obtain an ajimycin crystal and a preparation method thereof.

An object of this invention is to provide an ajimycin crystal having brilliant fluidity and a proper amount of non-crystal water. To be specific,

the ajimycin crystal in the present invention contains less than 4% of adsorption water, and has the following features:

1. The infrared spectrum (KBr) shows the frequencies of the following groups:

Wave number cm^{-1}	group
1000-1200	C-O-C
1340-1460	-CH2
1719	-C-O
1380	N-CH3
2780-3020	-CH3
3400-3600	-OH, H2O

There are characteristic absorption peaks at 3600-3400cm^{-1}, 3020-2780cm^{-1}, 1719cm^{-1}, 1460-1340cm^{-1}, 1380cm^{-1} and 1200-1000cm^{-1}.

2. Ultraviolet absorption spectrum:

The ajimycin crystal of the present invention has a maximum absorption wavelength λmax=207.7nm

3. Analysis on elements:

Theoretical values(%)	C60.93	H9.69	N3.74
Actually tested values(%)	C59.49	H9.87	N3.74

4. Analysis on heat differences:

Comparing the DSC curve of the sample with that of the imported control, one can see that the two curves are substantially the same, except that the melting heat of the sample is only a half of that of the imported control: 5.83 calories/t (sample) and 13.14 calories/gram (imported control). The comparison shows that the ajimycin (sample) of the present invention contains adsorption water.

5. Nuclear magnetic resonance spectrum (NMR)

a. H-NMR has the following features:

'H-NMR(CDCl2) δ is 2.28[3'-N(CH3)2], 2.34(9a-NCH3);

b. C-NMR has the following main features:

^{13}C-NMR(CDCl3) δ is 178.91(C-1), 78.14 and 83.32(C-3, C-5), 36.14(9a-NCH3), 40.34[3'-NC(CH3)2].

6. Thermogravimetric analysis (TGA)

As the temperature arises, the gravity of the sample reduces evenly from 50 to 105℃.

7. X-ray diffraction:

θ °	interplanar spacing d(A)	I/10	θ °	interplanar spacing d(A)	I/10
7.58	11.65	7	19.04	4.66	15
7.80	11.33	26	19.62	4.52	12
9.40	9.40	20	20.40	4.35	26
9.80	9.02	100	20.96	4.24	14
10.06	8.79	5	21.76	4.08	10
11.20	7.89	29	22.60	3.93	9
11.42	7.74	9	23.46	3.79	7
11.94	7.41	7	24.52	3.63	8
12.40	7.09	23	24.76	3.60	9
13.94	6.35	11	25.22	3.53	7
15.72	5.63	15	29.50	3.03	5
16.08	5.51	9	31.24	2.86	5
16.58	5.34	8	32.76	2.73	4
18.42	4.81	9	34.86	2.57	4
18.86	4.70	19	35.14	2.55	4

Another object of this invention is to provide a method for preparing said ajimycin crystal, which mainly comprises dissolving a water-contained

ajimycin in a mixture of a water-soluble organic solvent and water, crystallizing and drying it.

The detailed steps and technological conditions for said preparation method are as follows:

The relative weight ratio of the water-contained ajimicin:water:water-soluble organic solvent is 1: 30-1000: 9-16;

The water-soluble organic solvent is selected from the group consisting of ethanol, acetone, iso-propanol, propanol, 1,2-propylene glycol, 1,2-propylene glycol, propionitrile, 2-chlorohydrin, N,N,N',N'-tetramethylurea, N-methylpyrrolidone, allyl alcohol or a mixture thereof;

The organic solvent is preferably acetone, ethanol or a mixture thereof;

The drying is vacuum drying for 4 to 5 hours.

The present invention is further illustrated with the examples provided hereinafter:

The table below shows the experimental results concerning the stability of the ajimycin crystal of the present invention (at a temperature of 10-32 ℃, and a dampness of 25-80%):

Storage time (month)	Amount of water(%)
0	3.3
1	3.4
3	3.5
6	3.5
12	3.6
17	3.6

It can be seen from the above data that, sampling the ajimycin of the present invention after 0, 1, 3, 6, 12 and 17 month(s), one measures said

ajimycin and finds that the amount of water contained therein is 3 to 4%. An amount of less than 4% may satisfy the requirement of an industrial production.

With respect to the preparation of ajimycin crystal according to the examples:

(1) 100 grams of water-contained ajimycin prepared according to the U.S. patents US4517359 and US4474768 was dissolved at 50℃ in 400ml of acetone, to which water was added dropwise up to 600ml. The mixture was stirred slowly for five hours at a speed of 200 to 300 rotates/minute, cooled to an ambient temperature and filtered. It was then washed with 3 ×100ml of a mixture in which acetone:water=1:2, and vacuum dried at 40-50℃ for 4-5 hours (0.08MPa-0.09MPa) until 3.0-4.0% of water is left, to yield 86.1 grams of ajimycin crystal.

(2) 100 grams of water-contained ajimycin prepared according to the U.S. patents US4517359 and US4474768 was dissolved at 50℃ in a mixture of 400ml ethanol and 400ml of acetone, to which water was added dropwise up to 600ml. The mixture was stirred slowly for five hours at a speed of 200 to 300 rotates/minute, cooled to an ambient temperature and filtered. It was then washed with 3×100ml of a detergent liquid in which ethanol:acetone:water=1:1:4, and vacuum dried at 40-50℃ for 4-5 hours (0.08MPa-0.09MPa) until 3.0-4.0% of water is left, to yield 86.1g of ajimycin crystal.

Hereinafter are the substantive features and notable progress of the present invention:

The ajimycin crystal provided by the present invention is a stable compound. Compared with the dihydrate ajimycin crystal imported abroad, the ajimycin crystal of the present invention has brilliant fluidity and is suitable for preparing pharmaceutical preparations. In addition, since the ajimycin crystal of the present invention is a non-dihydrate crystallized-type Ajimycin, it has excellent bioavailability in pharmaceutical preparations. Moreover, the preparation method of this invention uses easily obtained reagent, and is convenient to operate.

CPCH0161523

Reference document CN1161971

Claims

1. An ajimycin crystallization, characterized in that it comprises less than 4% of adsorption water at an ambient temperature.

2. An ajimycin crystallization according to claim 1, characterized in that it has the following features: UV-absorption spectrum λmax is 207.7nm; ^{1}H-NMR(CDCl2) δ is 2.28[3'-N(CH3)2], 2.34(9a-NCH3); ^{13}C-NMR(CDCl3) δ is 178.91(C-1), 78.14 and 83.32(C-3, C-5), 36.14(9a-NCH3), 40.34[3'-NC(CH3)2]; IR: testing said ajimycin crystallization using potassium bromide and finding that it has characteristic absorption peaks at 3600-3400cm^{-1}, 3020-2780cm^{-1}, 1719cm^{-1}, 1460-1340cm^{-1}, 1380cm^{-1} and 1200-1000cm^{-1}.

3. A process for preparing an ajimicin crystallization according to claim 1, characterized in that said ajimicin crystallization is obtained by dissolving a water-contained ajimicin in the mixture of water soluble organic solvent and water, crystallizing and then drying the resulted mixture.

4. A process according to claim 3, wherein the relative weight ratio of water-contained ajimicin:water:water soluble organic solvent is 1: 30-1000: 9-16.

5. A process according to claim 3 or 4, characterized in that the water soluble organic solvent is selected from the group consisting of ethanol, acetone, iso-propanol, propanol, 1,2-propylene glycol, propionitrile, 2-chlorohydrin, N,N,N',N'-tetramethylurea, N-methylpyrrolidone, allyl alcohol or a mixture thereof.

6. A process according to claim 4, characterized in that the organic solvent is preferably acetone, ethanol or a mixture thereof.

7. A process according to claim 3, characterized in that the drying is vacuum drying for 4 to 5 hours.